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RECENT ADVANCES IN OUR KNOWLEDGE OF SLEEPING SICKNESS.

BY

ARTHUR G. BAGSHAWE, M.B., D.P.H. (Cantab.)

(Paper read at a Meeting of the Society of Tropical Medicine and Hygiene, Friday, October 15th, 1909.)

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Introduction.—In the paper I have the honour of reading to-night I have taken as *recent* work which has been published in the last twelve months. The *advances* which I have endeavoured to chronicle are such as have an immediate bearing on the prevention or cure of Sleeping Sickness. *Sleeping Sickness* I have considered as meaning infection in all its stages by *Trypanosoma gambiense.* I have gone beyond my text in suggesting

openings for investigation, for it is obvious that such a paper as this is of value, if at all, in so far as it indicates not only the ground which has been won but also the points at which assaults promise most success.

The course of human trypanosomiasis has been commonly divided into stages according to the symptoms. A convenient classification is that of the members of the French Sleeping Sickness Commission, G. MARTIN,[1] LEBŒUF and ROUBAUD, who have lately published in a large volume the results of two years' work in French Congo. They distinguish *cas en bon état*, persons who have no symptoms whatever of trypanosome infection; *cas suspects*, persons who have symptoms which lead to further investigation; and *cas cliniques*, cases which can be diagnosed from symptoms alone. A more accurate division which they make when it is possible depends on the result of spinal puncture. If evidence of invasion of the subarachnoid space by trypanosomes is thus obtained the patient is at the second or third stage; if not, he is at the first. By this means some of the patients with no symptoms are shown to be actually at the second stage. In the course of this paper when speak of patients in the first stage I mean those whose cerebro-spinal fluid is normal, or believed to be normal.

TRANSMISSION.

Glossina palpalis.—Since the year 1903, we have known that *Glossina palpalis* is the transmitter of human trypanosomiasis, but it is only recently that we have acquired accurate knowledge of the conditions of transmission. As is generally known, KLEINE,[2] in his paper published in March of this year, showed that after the fly ingests the trypanosome (in this case *brucei*) an interval of eighteen

or twenty days occurs, during which it is non-infective, but that after that period it is able to infect susceptible animals. His observations were soon confirmed by BRUCE[3] for *T. gambiense*, and there is every probability that some flies remain infective for the rest of their lives. Infection by interrupted feeding or with an interval of a few minutes is, of course, possible, but it seems to me that it must be an unusual occurrence, for trypanosomes are as a rule rare in the circulation, and the quantity of blood contained in the proboscis-tube is so minute that the chance of any trypanosomes being contained therein is small. Sir DAVID BRUCE,[4] however, still believes that the mechanical method is by far the commoner.

KLEINE[5] has published figures of what must be regarded as *T. gambiense* in the alimentary tract of flies reared from the pupa, fed at first on animals infected with that trypanosome and afterwards on healthy animals. The forms show a marked differentiation. He has found parasites in the salivary glands as well, but regards their presence there as accidental rather than as bringing tsetse into line with anopheles. He has obtained no evidence of hereditary or germinal infection.

BRUCE[4] and his colleagues have made a very interesting observation; they introduced under the skin of a monkey a tiny drop of fluid from the gut of a fly fed seventy-five days previously on an animal infected with *Trypanosoma gambiense* and afterwards on healthy animals. The fluid was swarming with trypanosomes. Eight days later the monkey showed infection.

We know, therefore, that the trypanosomes ingested by the fly undergo some kind of development, but whether a sexual process occurs, or there is merely such a multiplication as is seen in cultures, we are at present ignorant. If

it is found that the trypanosomes are not able at all stages to infect the fly, as TODD[6] suggests, the hypothesis that a sexual stage occurs would receive indirect support.

KLEINE[5] found that of 410 flies which had fed on animals infected with *T. gambiense* twenty-two became infected, that is, five per cent.; since, however, about half of his flies died early in captivity he thought the percentage might be doubled. Whether ten represents the highest percentage that one would find in nature is, of course, uncertain. STUHLMANN,[7] whose work was done with *Trypansoma brucei* and *Glossina fusca*, infected about the same percentage. KLEINE'S flies had drawn their infection from monkeys, which were possibly at different stages of the disease, and perhaps not equally infective.

Experiments to ascertain if *G. morsitans*, or other species of *Glossina*, is able to convey *T. gambiense* after a similar interval will doubtless be undertaken. Should, however, these be successful there is no reason to anticipate an extension of the disease to *palpalis*-free regions. All the observations made hitherto support the thesis that Sleeping Sickness does not become endemic except in *palpalis* areas.

There are two other possible means of communicating the disease which have supporters—sexual coitus and blood-sucking insects other than tsetse-flies.

Sexual coitus.—The former hypothesis was brought forward by KOCH[8] and KUDICKE to explain the occurrence of the disease in women who lived in a *palpalis*-free area and said that they had never left it. Lately, KUDICKE[9] has stated that he has had forty-four of such female patients under treatment. HODGES, in an unpublished Memorandum, suggested an explanation of such cases.

He wrote: "When the epidemic first swept through the lake-shore district the men, whose employments naturally carried them into the greatest danger, usually suffered first. As the men weakened, their occupations, such as canoeing, were in part taken up by the women, who then ran greater risks and more often contracted the disease, while many of their husbands by this time had either died from it or showed obvious symptoms of its presence." KUDICKE, by introducing blood from an infected monkey into the vagina of an uninfected monkey, with careful precautions to avoid injury, brought about an infection. This observation, if confirmed, would suggest the possibility, in the case of a wound or ruptured blood-vessel of the penis, of such an occurrence in man. Here may be cited an observation of MANTEUFEL.[10] He found that if he put blood containing trypanosomes on a patch of unshaven sound skin the size of a florin, allowed the blood to dry and covered the patch with collodion, in the greater number of animals infection followed. He suggested as a reason why trypanosomes do not usually pass through the skin or mucous membrane the presence of some antibody. There are no records in favour of KOCH's hypothesis from other parts of Africa.

Mosquitos, etc.—The members of the Sleeping Sickness Commission in French Congo bring forward evidence in favour of the transmission of Sleeping Sickness by insects other than *Glossina*, especially mosquitos of the genera *Mansonia* and *Stegomyia*. This view, expressed in March of last year, is repeated and emphasized in their complete Report. They regard *Glossina palpalis* as the principal agent of infection, but think that mosquitos and probably other biting insects are "important auxil-

iaries," conveying infection in each hut from person to person during the night. They say that in regions where the natives nurse their sick in their own houses the disease spreads with much greater rapidity than in those where they drive them away. They give instances of one member of a family after another becoming infected, and quote cases in which a native was saved from infection in their belief by the use of a mosquito net. They found Sleeping Sickness extremely prevalent in marshy districts where *Mansonia* abounded, and attribute to this method of infection, in some instances, the annihilation of whole villages.

Examination of the data shows that in nearly all the cases there was a *palpalis* area at hand or within a few miles, and in some instances where the disease spread with great rapidity it is stated that it was of recent introduction and that the natives were badly nourished, either of which would be efficient cause of a severe epidemic such as lately raged in Busoga. It is easy to understand why the disease spreads more rapidly when the sick man remains in the village, for if he is driven away he is no longer preyed on by *palpalis*, or at least not by the same flies which bite his fellow-villagers, and moreover his early death removes the source of infection altogether.

Granted the occurrence of this method of transmission, it is quite impossible to form any conclusion as to its relative importance if the epidemics studied are close to *palpalis* areas. Under these circumstances any such attempt is mere conjecture. Attention should be concentrated on sporadic cases, patients living out of reach of any species of tsetse, and watch must be kept for signs of the disease in inmates of the same hut. I cannot but think that the French observers ascribe to these

"auxiliaries" a more important part than they really play. When we consider that imported cases of Sleeping Sickness never caused epidemics in the New World; that the disease wherever it is, endemic or epidemic, hugs the shores of *palpalis*-haunted lakes and rivers; that in Uganda inland from the Victoria Nyanza out of reach of tsetse-flies, no instance of infection from a sporadic case has come to light—we must, I think, demand more strict evidence than the French have given us. There are, however, a few cases recorded where the intervention of *palpalis*, or indeed of any species of *Glossina*, may, for one reason or another, be excluded, and one must admit that in these rare instances the intermediary was some other insect.*

I shall not refer here to the experiments on transmission of *T. brucei* carried out by various investigators with mosquitos and *Stomoxys*. They have, of course, proved the possibility of such an occurrence.

Diagnosis.

The diagnosis cannot, of course, be considered as established unless the trypanosome is found in one or other of the body fluids. As to the course which is best adapted for its discovery there has been some difference of opinion. The members of the French Commission have recently published statistics based on the examination of 459 infected persons, and since these examinations have evidently been conducted with much care, and the number of cases is large, the figures deserve careful study. One of their tables is appended:—

* The cases recorded by the French Commission should be studied in the fine work which they have lately published.

Table from "La Maladie du Sommeil au Congo Français."

(Martin, Lebœuf, Roubaud. *Paris.* 1909.)

	Examen direct du sang.	Centrifugation du sang.	Sang Total.	*Diagnostic ganglionnaire complét.	Ponction lombaire.
Nombre d'examens	417	100		400	167
Résultats positifs	152	92		353	120
Pourcentages	36·45	92	96·82	88·25	71·85

* By this expression the authors mean that a gland of each group (cervical, axillary, inguinal, etc.) was, if necessary, punctured.

Blood.—The high percentage of success obtained by direct examination of the blood will be at once noted. The films were wet; $\frac{7}{8}$-in. coverslips were used, a mechanical stage and a magnification of 276 diameters. Ten minutes were allowed for the scrutiny, and a second slide was, as a rule, not examined. The direct blood method was that by which trypanosomes were found in nine out of twelve Europeans in the Congo who were recognised to be infected. It is worth noting that in some cases where in a film of blood from one hand no trypanosomes were found, in a film from the other they were detected. By centrifugation of blood in twelve cases at the first stage trypanosomes were found in every one.

Glands.—The glands of 400 infected persons were examined in turn. The parasites were found most often in the cervical glands, 73 per cent.; next in the submaxmillary, 69 per cent.; and in the axillary, epitrochlear and inguinal, about 50 per cent. To determine the relative

frequency with which trypanosomes were contained in the different groups, a gland of each was punctured in seventy-eight patients; the cervical group headed the list, but was run very close by the inguinal—71 per cent. and 66 per cent. Seeing that in 11 per cent. of infected persons trypanosomes could not be found in the glands, the percentage of *puncturable* glands in the patients was studied; in the case of inguinal it was 89, in that of the cervical and submaxillary, 87. The authors write: "In our 459 cases of infection we have been unable to do gland puncture fifty-nine times, *i.e.*, in 12·8 per cent., either because the glands were too small, or because they did not exist." This statement is of great importance. It means, of course, that if one relies on gland puncture alone for a diagnosis of human trypanosomiasis at least twelve cases in a hundred will be missed because puncture cannot be done. Some of these twelve will have other signs of the disease; others will not. The figures of which the tables are made up are taken from patients examined under the best conditions by all known methods. Let us take another set of figures. LEBŒUF, who travelled through part of French Congo studying the disease, made use of gland puncture and direct blood examination only. He examined 552 persons, and trypanosomes were found in the glands of eighty. Each group of glands was examined, and 264 punctures were made. In eleven cases in which the glands were puncturable, but he was unable to find trypanosomes in them, they were found in the blood, *i.e.*, in 12 per cent. of the persons recognised as infected. Of these eleven, six belonged to the *bon état* class, *i.e.*, they were in apparent health. It appears, then, that if gland puncture alone is employed, even though it is carried

out with the greatest completeness and care, twelve out of a hundred patients will be passed over, and that, even if clinical signs are watched for as well, between six and seven per cent. will escape detection; and this when the examination is made by an expert. I have gone into this part of the subject at some length, because there seems to be a general impression that gland enlargement and gland puncture are by themselves an efficient sign and means of diagnosis of Sleeping Sickness; clearly, it is not the case. Examination of the blood must never be neglected, and it is especially important, for by its aid only can be discovered the very early, and therefore curable, cases. Those whose business it is to weed out the infected natives in a community should study these figures.

Cerebro-spinal fluid.—The results obtained by the French Commission with lumbar puncture in supposed early cases are remarkable; they examined the cerebro-spinal fluid of nineteen persons in apparent health with no symptoms whatever, and in five instances they found trypanosomes. They add that no case in which a trace of blood was found in the fluid is included in their statistics. This shows that until one has examined the cerebro-spinal fluid it is impossible to be sure that a patient is at the first stage.

Broden[11] and Rodhain have made a special study of the cerebro-spinal fluid in trypanosomiasis; they regard the presence or absence of trypanosomes as of quite secondary importance, and for this reason collect only 5 cc. of the fluid. They count the white cells and study their character. A mere increase of small lymphocytes (five per cubic millimetre being taken as normal) is found in early cases, and Broden and Rodhain think that this increase can be detected before it is possible to find trypanosomes.

In later cases there are found also muriform cells, and, later still, myelocytes.

A histological study is much needed of the central nervous symptoms of persons who have died at an early period of their infection. It may be that changes in the membranes would be detected in quite early cases. L. MARTIN and DARRÉ write: "From the beginning of trypanosomiasis the meninges are in a state of reaction."

Auto-agglutination of the red blood corpuscles.—Here again LEBŒUF, of the French Commission, has added to our knowledge. Among his 552 cases, in ninety-one of whom trypanosomes were found in the blood or glands, while all of these showed the phenomenon in a marked degree, in forty-eight others it was present also. Some were almost certainly infected, as could be judged from the symptoms; if lumbar puncture had been done and the blood centrifuged, doubtless trypanosomes would have been found in them. Were all the forty-eight infected? LEBŒUF does not commit himself to an opinion. It seems doubtful, however, whether well-marked auto-agglutination ever occurs in African natives apart from an infection by *Trypanosoma gambiense*. It is said to occur in certain forms of icterus due to haemolysis (L. Martin[12] and Darré). More attention should be paid to the subject, for auto-agglutination can be detected before recourse is had to the microscope, and, were it shown to be trustworthy, would be a simple and therefore valuable means of diagnosis. In any case we have in auto-agglutination an added reason for the examination of fresh blood films.

Test animals.—Till recently the test animals used for Sleeping Sickness were not very reliable. THIROUX[13] and D'ANFREVILLE have found that a species of *Cercopithecus*

(C. ruber or *patas)*, widely spread in Tropical Africa, is very susceptible to infection by *T. gambiense*. Monkeys inoculated from patients showed infection in from eleven to eighteen days. They point out that in the case of inoculation of a monkey, one can use many times the volume of fluid which could be submitted to centrifuga tion, an obvious advantage. This method has its uses, but, in my opinion, for the original diagnosis should be rarely necessary.

Culture on artificial media and complement fixation are diagnostic methods of the future.

Gland palpation.—When one is confronted with the task of estimating the percentage of infection in a community and of weeding out the trypanosome carriers, it is clearly impossible to employ microscopical methods in every case, and it is usual to rely on gland palpation for the separation of the natives who are to be examined more fully. It is admitted that this is not a perfect method. The difficulty is not only that infected persons at an early stage are without enlarged glands, but also that there are other conditions which cause adenitis, and though the glands due to trypanosomiasis have a peculiar character which can be recognised by a skilled observer when it is typically present, this character may be masked. The French Commission found that whereas under treatment some glands diminished in size, others did not, and they concluded that the enlargement of these, though they often contained trypanosomes, was due to other causes. There are, moreover, reasons for believing that in some cases the swelling of the glands is never great. We have no data which would indicate to us the interval between the first appearance of trypanosomes in the blood and the time when the glands become

large enough to puncture; it probably varies. HECKENROTH[14] mentions the case of a boy who had slight suborbital œdema, and in whose blood trypanosomes were found. Not till a year later did any glands become puncturable. The diminution in volume that occurs at a later stage, whether the result of treatment or not, is well known and must always be borne in mind. The fact that a single injection of an organic arsenical, such as atoxyl, may cause such a retrogression of glands that they cease in a few weeks to be puncturable, must always be present to workers in Africa, for there are now many such persons abroad. As a means of separation of possibly infected from probably uninfected natives, gland palpation will always be of use; but I doubt the value of statistics of gland enlargement when such a factor as the frequency of other conditions causing adenitis is unknown. If some observer, whose lot it is to examine a large number of natives with a view to checking the movements of the infected, were to palpate the glands and examine a blood film (macroscopically) in every instance, controlling the results by the various microscopical methods, and were to publish his figures, he would materially advance our knowledge. Recent work confirms the observations of DUTTON[15] and TODD that the larger the glands the more likely are trypanosomes to be found in them.

HECKENROTH, who examined many cases of trypanosomiasis in French Congo, considers œdema at least as valuable an early sign as gland enlargement.

The French observers bring out another point of interest. LEBŒUF on seven occasions found a *Microfilaria perstans* in a punctured gland. Three of these glands contained trypanosomes also; in the other four

patients there was marked glandular enlargement, of the cervical group in three cases. No trace of blood accompanied the embryos. It is possible then, that the presence of these blood worms may account for some cases of pronounced gland enlargement.

Symptoms.

An excellent clinical study of the disease is published in the French Report. Naturally the recent advances in this part of the subject are not numerous. The French[12 and 16] observers have published papers on the nervous manifestations of Sleeping Sickness—acute meningitis occurring in the second, rarely in the first, stage of the disease, perhaps before a diagnosis has been made; and the so-called cerebral and medullary forms. The cerebral forms they classify as diffuse and circumscribed. The former are manifested by mental and meningeal symptoms, sub-acute in character. There is loss of the intellectual faculties. In the circumscribed forms there is irritation of the cortex leading to convulsions or paralysis. Both forms are incurable. The medullary or spinal forms are characterised by paraplegia, with some loss of sensation and bladder troubles. These symptoms progress slowly and respond well to treatment. Hodges, in a report about to be published, remarks on the increase of cerebral symptoms in Uganda. "Paralysis, paresis and epileptiform convulsions," he writes, "which among untreated cases occurred in a small percentage are now commonly met with, and are often the precursors of sudden death, which itself was very exceptional before the use of organic arsenic. Sudden or rapid death, in fact, generally preceded by cerebral symptoms, would appear now to be

almost the rule among such cases as have received full courses of organic arsenic, while the prolonged lethargic stage which almost invariably marked the end of untreated cases is either scarcely noticeable or absent." (*Vide* also THIROUX.[17]) I am unable to suggest any reason for this.

Such symptoms as deep hyperæsthesia (Kérandel's sign) and iritis or cyclitis do not come within my period.

TREATMENT.

Many papers on this branch of my subject have been published in the last twelve months. The number of new drugs employed has not been large; it includes *arsacetin* (the acetyl derivative of arsanilic acid) *arsenophenylglycin* and *p. aminophenylstibinic* acid, which corresponds to arsanilic acid, with antimony substituted for arsenic in the molecule. Experience has been gained in the use of the older drugs, such as atoxyl or soamin, with or without mercury; orpiment; tartar emetic, etc.

Arsanilate (Atoxyl or Soamin).—It is certain that these substances are best administered by hypodermic injection. BRODEN[11] and RODHAIN, who gave atoxyl by the mouth to seventy-nine patients, concluded that the method was suited only for persons with a normal cerebro-spinal fluid, and that in any case if improvement was not rapid injections should be given. From the evidence we have, it seems that nothing is gained by injection of the drug into the spinal canal, and I believe I am right in saying that this is not an established procedure in any disease.

In the great majority of cases arsanilate causes the parasites to disappear promptly from the blood and glands and not to reappear there while treatment lasts; there

are, however, exceptions. L. MARTIN[18] and DARRÉ had two European patients in whom the trypanosomes were insensitive to atoxyl; during its administration parasites were to be found in their blood and circinate erythema appeared; their eighteen other patients reacted well to the drug. AYRES KOPKE[19] reports a case, that of a Portuguese in whose blood trypanosomes persisted in spite of injections of atoxyl and, later, arsacetin. I know of a fourth case in a European (unpublished); another is mentioned by EHRLICH.[20] Here, then, are five European cases in which trypanosomes persisted in the blood in spite of atoxyl injections, and the comparative lack of record of such an occurrence in natives is probably due to the fact that they are not so closely studied. What is the nature of this insensitiveness of the parasites? Is the resistance specific? EHRLICH and KOPKE had no doubt that it was in their cases. Fortunately such resistance is not common, and there is no evidence that a chemo-resistant strain keeps its property when transferred by an insect to a fresh individual. It is probable that serum-resistant strains, that is, strains resistant to antibodies, are of much greater importance in the treatment of man than chemo-resistant strains. We are on the threshold of our knowledge of serum resistance.

Cases of reappearance of parasites in the glands are rare.

Have any cures resulted from the use of atoxyl alone? It is still uncertain. BRODEN and RODHAIN are convinced that atoxyl can cure a large number of patients at the first stage. The members of the French Commission express themselves in the same sense. Two things must, however, be borne in mind: (1) The interval during which a patient who afterwards relapses may remain well is not yet known; G. MARTIN[21] and LEBŒUF record

a relapse after fifteen months' perfect health; trypanosomes were then found in the cerebro-spinal fluid; this was a case treated at the first stage. And NATTAN-LARRIER[22] reports the cases of three Europeans who were not treated at all: one remained well for seventeen months, the second for two years, and the third for three years, after which he relapsed. It is not stated whether they were examined for trypanosomes during that period. (2) We must remember that the cases of apparent cure which have been longest under observation were treated before the atoxyl era. HODGES, in the Report mentioned above, writes:—"The number of early cases which have maintained their improvement has steadily decreased, and the number of cases likely to be permanently cured is now inconsiderable." If there are any persons who have made a recovery I would be inclined to attribute the happy event to their power of resistance rather than to the doses of atoxyl which may have been administered.

The arsanilates, and especially atoxyl, are not without their dangers; there are many recorded cases of blindness following the use of atoxyl.[23] Much attention has lately been paid to this subject, but it is not yet clear whether the lesion is central or in the retina. The first symptom is contraction of the fields of vision; the fields, therefore, should be tested from time to time in all patients who are taking arsanilates. It is possible that persons infected with *T. gambiense* are predisposed to such lesions; they have not been noticed in early cases. In Uganda all the victims seem to have been at a fairly advanced stage, and BRODEN and RODHAIN found that of their patients who became blind all had either typical symptoms of Sleeping Sickness or an altered cerebro-spinal

fluid; consequently they recommend a smaller dose for patients at the later stage than for the earlier cases. It seems that loss of vision is less frequent, if it occurs at all, after the use of soamin, which has, of course, a chemical formula identical with atoxyl.

How long should a course of arsanilate last? This is a difficult question to answer. BRODEN and RODHAIN are doubtful if it is of any use to resume or continue its employment after a relapse. It must be remembered that to detect a relapse it is not sufficient to examine the blood; the cerebro-spinal fluid must be examined from time to time. There are reasons for believing that, apart from the possible development of resistance by the parasites, the prolongation of a course beyond a certain limit, not at present defined, leads to supersensitiveness on the part of the patient. In Uganda, at any rate, the administration of organic arsenicals for several months in succession has been abandoned.

When the arsanilates came into use for Sleeping Sickness it was hoped that they would act by killing off the trypanosomes in the body, that is to say, as sterilizing agents, as they appear to do in experiments on small animals. This hope has been disappointed, probably because we are unable to give the drug in such doses as will cause the requisite concentration of the trypanocidal substance. Prof. BENJAMIN MOORE[24] considers that the size of man, as in the case of large animals, is against his cure; he shows that the dose which can be given depends on the area of body surface and that therefore small animals have an advantage. He believes also that the dosage depends on the area of cells lining the intestine, for these take up the arsanilate, and if the drug is present in too great concentration they are killed.

Antimony.—Tartar emetic or the corresponding sodium salt is now given intravenously to avoid the pain and re-action caused by injection into the tissues. This treatment alone is not effective for any length of time, possibly because of the rapid elimination of the drug. G. MARTIN,[25] LEBŒUF and RINGENBACH find that though it drives trypanosomes promptly from the blood they may be present in the cerebro-spinal fluid after many injections. Injections of finely divided metallic antimony in an oily emulsion, the so-called antimony cream, are so painful that they drive away the patient as well as the trypanosomes.

There is now, I think, a consensus of opinion that two or more drugs should be employed in combination. For this course there are three reasons:—(1) Experiments on animals have clearly demonstrated the advantage. (2) One can give a smaller, and, therefore, less dangerous dose of each drug than would otherwise be the case. (3) The researches of EHRLICH and others show that substances of different chemical groups combine with different parts of the protozoal cell. It is interesting to note that a drug which by itself has no action may become of value when it is associated with a powerful trypanocide; examples are mercury, and perhaps picric acid.

Arsanilate + mercury.—Many clinicians have tried this combination. HODGES and BRODEN, both of whom have had much experience, consider that it has no advantage over arsanilate alone. Van SOMEREN,[26] who injects soamin and perchloride of mercury simultaneously, thinks that the patients so treated do rather better than those who get soamin only. No one, however, speaks very favourably of the combination.

Arsanilate + orpiment is now being largely given. We are not yet able to form an idea of the value of this

combination. The use of an inorganic arsenical has two recommendations: (1) some of the early cases which have made an apparent recovery were thus treated, and (2) EHRLICH'S work tends to show that trypanosomes never become resistant to arsenic in this form.

Arsanilate + tartar emetic.— BRODEN and RODHAIN,[27] as well as the members of the French Commission, speak well of this combination, which at the present moment seems to be more effective than any other. The arsanilate is injected under the skin once a week, the antimony salt into a vein once or twice a week, or in series. THIROUX[28] finds that unpleasant symptoms after antimonial injection can be prevented by the previous administration of caffeine.

To come to the new drugs—*Arsacetin* has been used in 134 cases by ECKARD[29] in German East Africa. He finds that therapeutically it equals atoxyl, over which it has the advantage that it is much more stable. Unfortunately blindness occurs after its use; it is noted in three cases.

P. aminophenylstibinic acid has been given once with good effect (KOPKE[19]). In injections it is much too painful for general employment, but the fact that it is the antimony homologue of arsanilate makes its use promising as well as of interest.

Arsenophenylglycin is the most promising of all the organic arsenicals. We know that doses of one gram are well borne by man,[29 and 30] and that trypanosomes are banished from the blood and glands. More, at present, cannot be said. The advantage of this substance is that while the arsanilates and their derivatives have to undergo some change in the tissues, reduction in EHRLICH'S opinion, before they become trypanocidal, arsenophenyl-

glycin is already reduced, hence its toxicity is more constant for any given species of animal, for it does not depend on the varying amount of change effected by the animal tissues.

EHRLICH[31] has shown that to get a sterilizing effect, it is not necessary for all the parasites to be killed; it is sufficient if the drug so acts on that part of the trypanosome which is concerned with multiplication that the formation of new individuals ceases. He believes that arsenophenylglycin acts in this way. Here we have perhaps another explanation of the undoubted advantage of giving two or more drugs in association. One attacks the nuclear or chromidial apparatus, another the protoplasm, or as EHRLICH puts it, they combine with receptors situated in these different parts of the cell. EHRLICH himself says that arsenophenylglycin acts much more powerfully on infected guinea-pigs if another drug (tryparosan in this case) is associated with it. Since arsenophenylglycin is likely to be soon in general use, I will echo the warning given by EHRLICH against the use of this substance, *to begin with*, on patients who have relapsed after other treatment. He points out that such cases are very difficult to cure, so that the reputation of a new remedy may be blasted because it is expected to perform an impossible task. Any new drug, when once its claim to trial in human therapeutics has been established by a series of successes in animal infections, should be tested on untreated selected cases at an early stage of the disease; later, of course, the relapsed or advanced cases may share the benefit.

Dyes.—Treatment by dyes has not proved of much service in the human subject, but we may yet find one which is useful. I do not think parafuchsin in combina-

tion with the more powerful trypanocides has had an efficient trial, but tryparosan (Ehrlich) promises still better results because it is more effective in animals, and tends to attenuate the virulence of the trypanosomes.

It is probable that the trypanocides, even when they do not sterilize, increase the resisting power of the organism. They may assist in the production of immunity, as has been shown by animal experiment.

Serum.—Dr. Andrew Balfour,[32] acting on the idea that the cerebro-spinal fluid is lacking in trypanocidal substances, has suggested the introduction into the spinal canal of the patient's own serum, perhaps after a course of chemical treatment. The idea and the suggestion had been put forward, unknown to Balfour, by Thiroux[33] two years earlier. We have no record of the adoption of this plan.

General Measures.—One factor in treatment has, perhaps, been imperfectly realised, that is the importance of increasing the resistance of the patient, especially by a generous diet. The Members of the French Commission especially have emphasized this, and it is common knowledge that in time of scarcity or famine Sleeping Sickness becomes epidemic in places where it was previously present in an unobtrusive form. In Busoga, a province in Uganda in which the natives reached the segregation camp in half-starved condition, the results of treatment were much less favourable than in other camps. Bödeker,[34] in British East Africa, has treated a few cases with cod-liver oil in conjunction with soamin or atoxyl, and has reported favourably on them. Such treatment seems to me very reasonable, and I think cod-liver oil should be tried in a large series of cases. Dr. Daniels[35] has recently called attention to the importance

of increasing the resistance of the host in the protozoal as in the bacterial diseases. Similarly one must treat any condition which tends to drain the vitality of one's patient, *e.g.*, ankylostomiasis.

Prognosis.

It is at present impossible to set a term to the existence of a patient infected with *T. gambiense*, but we are able to gauge to some extent his power of reacting to treatment and whether there is any prospect of cure. Though patients at the first stage, treated or even untreated, may recover, it is extremely doubtful whether any person has ever recovered in whose cerebro-spinal fluid trypanosomes have been demonstrated, either by their presence or by the change they have brought about in the constitution of the fluid. Lumbar puncture, then, is essential if we are to give any sort of guess as to the future. If trypanosomes are found, or if there are certain cell changes in the cerebro-spinal fluid, one can say,—This man may live for years, but he is not likely to recover.—Similarly the result of treatment can be checked by lumbar puncture. The patient may be improved in his general condition and be apparently well, but the result of the puncture shows that the disease is progressing towards its fatal termination. Broden and Rodhain think that treatment should be continued as long as the cerebro-spinal fluid is abnormal; but that this is not a sure guide is shown by the observations of members of the French Commission who found that some cases at quite a late stage had a cerebro-spinal fluid which contained no trypanosomes and few cells. It is worth noting that the members of the French Commission were unable to find trypanosomes in the cerebro-spinal fluid of twenty-six out of 108 advanced cases,

i.e., 24 per cent. They do not say if lumbar puncture was repeated in any instance. Lumbar puncture has unfortunately three disadvantages: it is disliked by patients; the trypanosomes come and go in the fluid so that unless the typical cell changes are present one negative result is inconclusive; and there may be a risk of introducing trypanosomes into the sub-arachnoid space. Ayres Kopke[19] for this reason, in a case in which trypanosomes were very numerous in the blood, did not venture to puncture the membranes

As to the value of *auto-agglutination* for prognosis we are in want of data. In patients who have made an apparent recovery, auto-agglutination has become much less marked without wholly disappearing.

Thiroux[13] and d'Anfreville have found *Cercopithecus patas* a valuable test animal, when they wished to know if trypanosomes were present or not in a patient who had undergone a course of treatment. They inject 20-40 cc. of defibrinated blood into the monkey, and again if necessary after a month; if both inoculations are negative, lumbar puncture is done and the cerebro-spinal fluid injected into the monkey. Here again, for decisive information, one must do lumbar puncture. If this method proves to be as reliable as its authors believe, it will be very useful in Tropical Africa, for the species *ruber* or *patas* is widely spread.

Prophylaxis.

In the last twelve months few fresh preventive measures have been proposed. It is probable that when we know more of *Glossina palpalis*, its life history, breeding grounds, and natural enemies, we shall be able to devise more effective measures for its suppression or exter-

mination. At present we have, in the main, two alternatives: to avoid the fly or to clear the scrub which shelters it.

Citronella grass as a tsetsefuge has lost its reputation. From various quarters comes the report that the flies do not mind it at all, and one observer doubts if it gives off any smell except when it is crushed. The members of the French Commission insist on the necessity for the use of a mosquito net, and if their belief that mosquitos are important auxiliaries of *palpalis* finds confirmation, protection from these, and all biting insects, becomes absolutely necessary. They think also that all Europeans who serve in infected areas should be periodically examined, and seeing that a trypanosome infection at the beginning may be taken for malaria or some other fever, this seems a wise precaution.

ROUBAUD,[1] as a means of dealing with *G. palpalis*, recommends *partial* clearing or thinning of the vegetation which shelters the fly. It is generally recognised that complete clearing is not essential, that clean stemmed trees may be left if all the undergrowth is removed; but, if one may judge from photographs, ROUBAUD leaves much vegetation standing besides trees. His aim is to let the sun's rays reach the soil. The amount of clearing or thinning needed at any spot can always be determined by experiment, and I think it probable that in some instances more is done than is necessary. On the only occasion on which I had the opportunity of superintending such work, the flies disappeared when the vegetation on half the area marked out had been cut down. This is worth remembering, for it is costly to fight jungle on a large scale.

We have learnt, I think, that the preventive measures to be adopted are not the same for all parts of Tropical

Africa, that is to say, in one region, as Uganda or Rhodesia, it is found possible, and therefore best, to remove all natives from *palpalis* areas and to clear the vegetation in the neighbourhood of fords and watering places; in another, as Togoland, neither of these things can be done to a profitable extent, and it is sought to collect all the infected persons into fly-free camps; in a third, it may be that a system of inspection posts is of value. Even if our preventive measures fail, there are reasons for thinking that nature is slowly working, in Uganda for instance, to produce a state of toleration in the tissues of the persons infected. How this comes about, whether by an attenuation of the virulence of the trypanosome, by the weeding out of less resistant individuals, or by a combination of these factors, we do not know. To give one instance: BAKER in Uganda examined in January of this this year a native in whose case there was documentary evidence that trypanosomes were found in the blood in 1905. BAKER found trypanosomes in his glands. This man had had no treatment and had served in the King's African Rifles for three-and-a-half years without having ever been off duty for sickness. It is worth noting that the French Commission found marked differences in virulence of *T. gambiense* in man.

I have given you but a bald account of the recent advances in our knowledge of Sleeping Sickness. The extent of ground to be covered has prevented my straying into attractive by-paths. I think, however, that I have touched sufficient points for discussion.

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For summaries of these papers and for other references, see the *Bulletins of the Sleeping Sickness Bureau*, Nos. 1-10.

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